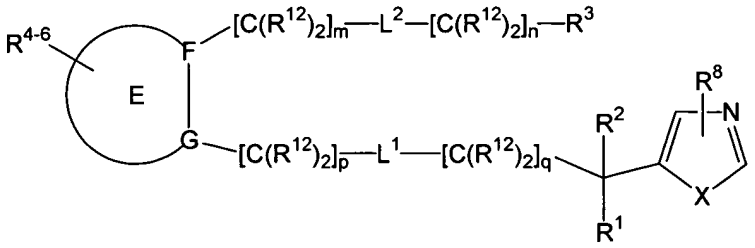
Amendments to the Claims

1 (Previously Amended). A compound of formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

E is a six-membered aromatic carbocyclic ring in which F and G are C;

L^1 is O;

L^2 is selected from the group consisting of a bond, C_2alkenylene, C_2 alkynylene, O, NR^9, C(O), S, S(O), SO_2, SO_2NR^9, NR^9SO_2, $C(O)NR^9$, $NR^9C(O)$, and CO_2;

X is NR^7;

R^1 is selected from the group consisting of aryl, arylalkyl, heterocycle, and (heterocycle)alkyl;

R^2 is selected from the group consisting of hydrogen, alkoxy, alkyl, amino, aminoalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, heterocycle, (heterocycle)alkyl, hydroxy, and hydroxyalkyl;

R^3 is selected from the group consisting of aryl, heterocycle, and cycloalkyl;

R^{4-6} are each independently selected from the group consisting of hydrogen, $NR^9C(O)$, $C(O)NR^9$, alkanoyl, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aminosulfonyl, aryl, arylalkyl, aryloxy, arylsulfonyl, azido, carboxy, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkoxy, haloalkyl, heterocycle, (heterocycle)alkyl, hydroxy, hydroxyalkyl, nitro, nitroalkyl, oxo, and thio(oxo);

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocycle, (heterocycle)alkyl, and trialkylsilyl;

R^9 is selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, amidoalkyl, aminoalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, carboxyalkyl, heterocycle, (heterocycle)alkyl, hydroxyalkyl, and a nitrogen protecting group;

each R^{12} is independently selected from the group consisting of hydrogen, alkoxy, alkyl, amino, halo, and hydroxy;

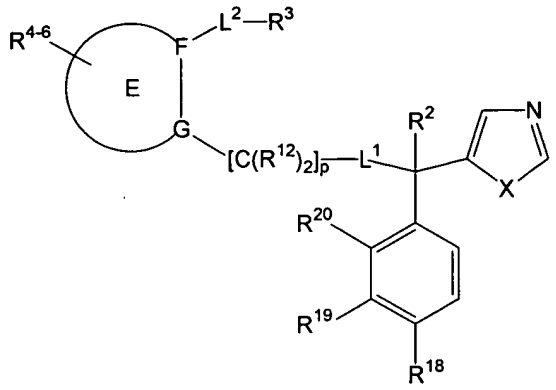
m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4; and

q is 0, 1, 2, 3 or 4.

2 (Original). A compound according to Claim 1 of formula (II)



(II),

or a therapeutically acceptable salt thereof, wherein

E, F, G, L^1, L^2, X, R^2, R^3, R^{4-6}, R^{12}, and p are as defined in Claim 1 and

R^{18}, R^{19}, and R^{20} are each independently selected from the group consisting of hydrogen, cyano, and halo.

3 (Previously Amended). A compound according to Claim 2 wherein

L^2 is selected from the group consisting of a bond, NR^9SO_2, and $C(O)NR^9$;

wherein each group is drawn with its left end attached to F and its right end attached to R^3;

R^2 is selected from the group consisting of hydrogen and hydroxy;

R^3 is selected from the group consisting of aryl and heterocycle;

R^{12} is hydrogen; and

p is 0 or 1.

18 (Previously Amended). A compound according to Claim 3 wherein one of R^{4-6} is cyano.

19 (Original). A compound according to Claim 18 wherein

R^{18} is cyano; and

R^{19} and R^{20} are hydrogen.

20 (Original). A compound according to Claim 19 selected from the group consisting of 6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3'-methoxy(1,1'-biphenyl)-3-carbonitrile;

6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3'-ethoxy(1,1'-biphenyl)-3-carbonitrile;

3-(1,3-benzodioxol-5-yl)-4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)benzonitrile;

3'-chloro-6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-carbonitrile;

N-(5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)phenyl)-2-thiophenesulfonamide;

N-(5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)phenyl)-4-methylbenzenesulfonamide;

5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-N-(4-methylpyridin-2-yl)benzamide;

N-(3-chlorophenyl)-5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)benzamide;

4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3-(6-oxo-1-propyl-1,6-dihydropyridin-3-yl)benzonitrile; and

4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3-(6-propoxypyridin-3-yl)benzonitrile.

21 (Previously Amended). A compound according to Claim 3 wherein one of R^{4-6} is halo.

22 (Original). A compound according to Claim 21 wherein R^3 is heterocycle.

23 (Original). A compound according to Claim 22 wherein

R^{18} is cyano; and

R^{19} and R^{20} are hydrogen.

24 (Original). A compound according to Claim 23 selected from the group consisting of 4-(((2-(1,3-benzodioxol-5-yl)-4-chlorobenzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile; and4-(((4-chloro-2-(5-formyl-2-thienyl)benzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile.

25 (Original). A compound according to Claim 21 wherein R^3 is aryl.

26 (Original). A compound according to Claim 25 wherein the aryl is unsubstituted or substituted with one substituent selected from the group consisting of alkanoyl, alkoxy, alkyl, amino, cyano, formyl, halo, and haloalkyl.

27 (Original). A compound according to Claim 26 wherein

R^{18} is cyano; and

R^{19} and R^{20} are hydrogen.

28 (Previously Amended). A compound according to Claim 27 selected from the group consisting of

4-(((2',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-2'-methyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-2'-methoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((3',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-methyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-methoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-fluoro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4-chloro-2-(1-naphthyl)benzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((3'-amino-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

3'-chloro-6'-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-carbonitrile;

4-(((2'-acetyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4'-acetyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4'-tert-butyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-ethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

N-(5'-chloro-2'-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-yl)acetamide;

4-(((5-chloro-4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile; and

4-(((5-chloro-3'-formyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile.

29 (Original). A compound according to Claim 25 wherein the aryl is substituted with two or three substituents independently selected from the group consisting of alkoxy, alkyl, and halo.

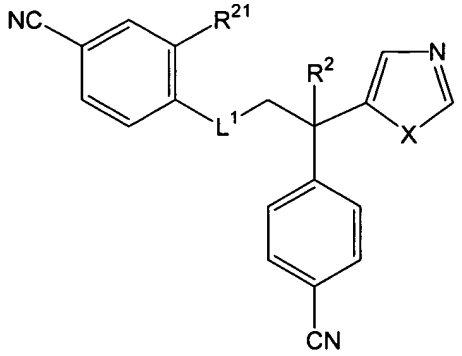
30 (Original). A compound according to Claim 29 wherein

R^{18} is cyano; and

R^{19} and R^{20} are hydrogen.

31 (Original). A compound according to Claim 30 selected from the group consisting of
4-(((5-chloro-3',4'-dimethyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-2',5'-dimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3',4'-dimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3',4',5'-trimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-((1-methyl-1H-imidazol-5-yl)((2',3',5-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile;
4-((1-methyl-1H-imidazol-5-yl)((3',5,5'-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile; and
4-((1-methyl-1H-imidazol-5-yl)((3',4',5-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile.

32 (Original). A compound according to Claim 1 of formula (III)



(III),

or a therapeutically acceptable salt thereof, wherein
L^1, X, and R^2 are as defined in Claim 1; and
R^{21} is selected from the group consisting of aryl and heterocycle.

33 (Previously Amended). A compound according to Claim 32 wherein
L^1 is O;
X is NR^7; and
R^2 is selected from the group consisting of amino, halo and hydroxy.

38 (Previously Amended). A compound according to Claim 33 wherein
R^2 is hydroxy; and
R^{21} is aryl.

39 (Original). A compound according to Claim 38 selected from the group consisting of 6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-methoxy-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',4'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-fluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',5'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3',4'-dichloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
3',5'-dichloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-fluoro-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(1-naphthyl)benzonitrile; and
(S)-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

40 (Previously Amended). A compound according to Claim 33 wherein
R^2 is hydroxy; and
R^{21} is heterocycle.

41 (Original). A compound according to Claim 40 selected from the group consisting of

3-(1,3-benzodioxol-5-yl)-4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)benzonitrile;
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-quinolin-8-ylbenzonitrile; and
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)benzonitrile.

42 (Previously Amended). A compound according to Claim 33 herein
R^2 is halo; and
R^{21} is aryl.

43 (Original). A compound according to Claim 42 selected from the group consisting of
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-methoxy-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',4'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-fluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',5'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3',4'-dichloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
3',5'-dichloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-fluoro-1,1'-biphenyl-3-carbonitrile; and
3'-chloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile.

44 (Previously Amended). A compound according to Claim 33 wherein
R^2 is halo; and
R^{21} is heterocycle.

45 (Original). A compound according to Claim 44 selected from the group consisting of 3-(1,3-benzodioxol-5-yl)-4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)benzonitrile;
4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-quinolin-8-ylbenzonitrile; and
4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)benzonitrile.

46 (Previously Amended). A compound according to Claim 33 wherein
R^2 is amino; and
R^{21} is aryl.

47 (Original). A compound according to Claim 46 which is 6-(2-amino-2-(4-cyanophenyl)-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

48 (Original). A compound which is 6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

49 (Original). A compound which is 6-((2S)-2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

50 (Original). A pharmaceutical composition comprising a compound of Claim 1 or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

51 (Original). A method for inhibiting farnesyltransferase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of Claim 1, or a therapeutically acceptable salt thereof.

52 (Currently Amended). A method for treating cancer **by inhibiting farnesyltransferase** in a patient in recognized need of such treatment comprising

administering to the patient a therapeutically acceptable amount of a compound of Claim 1, or a therapeutically acceptable salt thereof.

Rejections Under 35 U.S.C. 112

Claims 1, 3, 22, and 32 stand rejected under 35 U.S.C. 112, first paragraph, as the Examiner maintains that the specification is not enabling for claiming all heterocycles. Specifically, the Examiner states that the heterocylces in the examples are limited to pyridine, quinoline, and benzene dioxo, and that the breadth of the claim exceeds these examples.

Applicants traverse the rejection and respectfully request withdrawal of the same.

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F 2d 1557 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Examiner has provided only a bare allegation that one of ordinary skill in the art would have to undergo undue experimentation to make the compounds of the claimed invention. Since the rejection is devoid of a reasoned explanation as to why an artisan, guided by the teaching in the instant specification and the knowledge in the art, would not be able to practice the invention with routine experimentation, the rejection under 35 U.S.C. 112 cannot stand.

According to §2164.02 of the MPEP, "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus ***only where adequate reasons are advanced by the examiner*** to establish that a person skilled in the art could not use the genus as a whole without undue experimentation."

Although Applicants maintain that the Examiner has not established a reasonable basis to question enablement, the Applicants herein highlight the support for their genus claim. The application discloses schemes in conjunction with working examples that support claiming heterocycles generically. (See examples 29, 46 for thiophene; examples 23, 33, 55, 56, 79, 80, 89 for benzene dioxo; examples 59, 60 for quinoline; examples 87 and 92 for pyridine; and example 91 for dihydropyridine). In each of these examples the desired heterocycle is added to the core compound when it is coupled with the corresponding boronic acid in the presence of catalytic palladium and base. The chemistry follows the schemes (see especially scheme 1) and leaves no undue experimentation for one skilled in the art.

Since the Examiner has not met the requisite burden of proof for an enablement rejection, and since the Applicants have provided clear direction for one skilled in the art to practice the claimed invention without undue experimentation, Applicants respectfully

submit that the 35 U.S.C. 112 rejection of Claims 1, 3, 22, and 32 is improper and request withdrawal of the same.

Claim 52 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner states that the specification does not have any tests that enable that the compounds would treat "cancers." Furthermore, the Examiner maintains that cancers are of various types and all are not treatable by the same protein transfer Ras.

Applicants traverse the rejection and respectfully request withdrawal of the same.

Claim 52 has been amended to clarify that the Applicants claim methods of treating cancer that are caused or exacerbated by farnesyltransferase. Support for this amendment is found on pages 16-17 of the application as filed.

As to the Examiners concern that the specification does not have any tests that enable that the compounds would treat "cancers;" Applicants have demonstrated the inventive compounds are potent inhibitors of farnesyltransferase and that farnesyltransferase plays an important role in tumor formation and metastasis. Therefore, those skilled in the art would accept the *in vivo* test as a model enabling the claim that the compounds treat cancers caused or exacerbated by farnesyltransferase.

ACTION REQUESTED

For all the forgoing reasons, Applicants submit that Claims 1-3, 18-33, and 38-52 are in condition for allowance. To that end, the examiner is invited to contact the undersigned to schedule an Examiner Interview to discuss any matter.

Respectfully submitted,
Claiborne, *et al.*

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